IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant:	Jay A. Goldstein, Michael Rothman, and Whe-Yong Lo		
Serial No.:	10/691,928	Art Unit:	1616
Filed:	October 23, 2003	Examiner:	Nathan W. Schlientz
For:	*ANTIFUNGAL FORMULATIONS*		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of the claims in the Office Action mailed on April 14, 2009. A Notice of Appeal was filed July 13, 2009. A Petition for an Extension of Time for two months, up to and including November 13, 2009, accompanies this Appeal Brief. The Commissioner is hereby authorized to charge the fee for filing of this Appeal Brief and Petition for Extension of Time to Deposit Account No. 50-3129.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is the assignee, G&R Pharmaceuticals, LLC.

(2) RELATED APPEALS AND INTERFERENCES

A Notice of Appeal was filed in the present application on June 23, 2006. An Appeal Brief with a one month extension of time was filed on September 1, 2006. Prosecution was reopened and a non-final Office Action was mailed on December 4, 2006. The Appeal was reinstated with the filing of the Notice of Appeal on July 13, 2009.

(3) STATUS OF CLAIMS

Claims 1-17 are pending and on appeal. The text of each claim on appeal, as pending, is set forth in an Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

The claims were last amended in the Amendment filed December 6, 2007. An appendix sets forth the claims on appeal.

(5) SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1 defines a topical antifungal composition comprising:

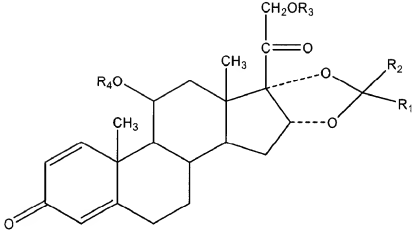
a) a therapeutically effective amount of an antifungal compound for treating a fungal disease or a pharmaceutically acceptable salt thereof; and

b) a therapeutically effective amount of a low to low-medium potency steroidal anti-inflammatory causing minimal skin atrophy, striae and hypopigmentation, in a concentration between 0.01 wt% and 5.0 wt%, and having a higher potency than 1 wt% hydrocortisone, and

c) a carrier suitable for administration of the antifungal compound and the steroidal anti-inflammatory to the skin,

wherein the composition does not cause the steroids to penetrate the skin and cause undesirable local side effects (page 2, lines 4-10; page 3, lines 19-21; page 5, lines 13-15; page 4, lines 15-16)

Dependent claim 2 specifies that the steroidal anti-inflammatory has the following structure:



wherein R_1, R_2, R_3, and R_4 taken independently can be H, C1-C10 alkyl, C1-C10 alkenyl, C3-C10 cycloalkyl, and phenyl groups; R_1 and R_2 taken together can be C3-C10 cycloalkyl; and R_3 and R_4 taken independently can be H, C1-C10 alkyl, C1-C10 alkenyl, C3-C10 cycloalkyl, phenyl, C7-C10 phenylalkyl, carboxylate, sulfonyl, phosphoryl, and phosphonyl groups (page 4, lines 15-25).

Dependent claim 3 specifies that R_1, R_2, R_3, and R_4 groups are independently H, CH_3, ethyl, propyl, phenyl, and phenylmethyl groups (page 4, lines 15-25).

Dependent claim 4 specifies that the steroidal anti-inflammatory is desonide and the antifungal compound is clotrimazole (page 3, lines 17-19)

Dependent claim 5 specifies that the composition contains 0.01 wt % to 5.0 wt % desonide (page 2, lines 20-21).

Dependent claim 6 specifies that the composition contains 0.1 wt % to 5 wt % clotrimazole (page 2, line 21).

Dependent claim 7 specifies that the steroidal anti-inflammatory is selected from the group consisting of Fluocinolone acetonide, Hydrocortisone valerate, Hydrocortisone butyrate, Alclometasone dipropionate, Desonide, and hydrocortisone probutate (page 5, lines 7-12).

Dependent claim 8 specifies that the antifungal is selected from the group consisting of polyene type antifungal agents and azole type antifungal agents (page 4, lines 1-5).

Dependent claim 9 specifies that the antifungal is selected from the group consisting of Amphoterican B, Nystatin, Flucytosin, Natamycin, Ketoconazole, Econoazole, Miconazole, Itraconazole, Fluconazole, Econazole, Clotrimazole, Griseofulvin, Oxiconazole, Terconazole, Tioconazole, Clotrimazole, Silver Sulfadiazine, Ciclopirox olamine, and Terbinafine (page 4, lines 5-13).

Dependent claim 10 specifies that the composition is formulated as a cream, ointment, gel, lotion, foam, powder, aerosol, spray, shampoo, or liquid solution (page 2, lines 22-24).

Dependent claim 11 specifies that the composition has a pH of about 3.5 to about 7.0 and further comprises: at least one solvent, at least one emollient, at least one humectant, at least one preservative, and at least one emulsifier; and optionally including an acid, base, or buffering agent to adjust the pH (page 4, lines 1-3).

Dependent claim 12 specifies that the solvent is selected from the group consisting of propylene glycol, butylene glycol, hexylene glycol, polyethylene glycols, polypropylene glycols, and polyurethane compounds; the emollient is selected from the group consisting of white petrolatum, mineral oil, propylene glycol dicaprylate, lower fatty acid esters and lower alkyl ethers of propylene glycol, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, stearic acid, cetyl esters wax, spermaceti wax, and white wax; the humectant is selected from the group consisting of glycerin and sorbitol; and the emulsifier is selected from the group consisting of glyceryl monostearate, glyceryl monoleate, stearic acid, polyoxyethylene cetyl ether, polyoxyethylene cetostearyl ether, polyoxyethylene stearyl ether, and polyethylene glycol stearate; the optional acid is selected from the group consisting of hydrochloric acid and phosphoric acid, the optional base is chosen from diethanolamine, triethanolamine, and sodium hydroxide, the optional buffering agent is chosen from monobasic sodium phosphate and dibasic sodium phosphate, and the preservative is chosen from benzyl alcohol, sodium benzoate and parabens (page 6, lines 1-16).

Dependent claim 13 specifies that the antifungal is in an amount effective to treat fungal disease selected from the group consisting of tinea pedis, tinea capitis, tinea corporis, tinea versicolor, scalp disorders, tinea cruris, and candidiasis (page 8, lines 11-13).

Dependent claim 17 specifies that the steroidal anti-inflammatory is not halogenated (page 2, lines 7-10; page 3, lines 19-21).

Independent claim 14 define a method of treating a fungal disease comprising administering to a subject in need of treatment the composition of any of claim 1-13 or 17, with a thin application of the composition two times per day to the affected areas (page 3, lines 16-19)

Dependent claim 15 specifies that the subject is a child of under 10 years old (original claim 15).

Dependent claim 16 specifies that the fungal disease is selected from the group consisting of tinea pedis, tinea capitis, tinea corporis, tinea versicolor, scalp disorders, tinea cruris, and candidiasis (page 3, lines 8-16 and original claim 16).

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues presented on appeal are:

(1) whether claims 1 and 8-13 are novel as required by 35 U.S.C. § 102(b) over U.S. Patent No. 6,075,056 to Quigley ("Quigley").

(2) whether claims 1-3, 8-13 and 17 are novel as required by 35 U.S.C. § 102(b) over U.S. Patent No. 6,238,683 to Burnett, et al. ("Burnett").

(3) whether claims 1-3 and 7-17 are non-obvious as required by 35 U.S.C. § 103(a) in view of U.S. Patent No. 6,075,056 to Quigley ("Quigley").

(4) whether claims 1-13 and 17 are non-obvious as required by 35 U.S.C. § 103(a) in view of Burnett and U.S. Patent No. 5,219,877 to Shah ("Shah").

(7) ARGUMENT

The Claimed Compositions

The claimed compositions relate to a combination of (1) low to mid-low potency steroidal anti-inflammatory and (2) an anti-fungal.

Dr. Goldstein has been a practicing dermatologist for many years. In the course of his treatment of patients, he has observed that many mid and high potency steroids cause serious side effects, including thinning of the skin, hypopigmentation, and striae distensae, which may be as significant of a problem as the presenting condition since fungal conditions take up to four weeks to respond to treatment. During this extended period of treatment, the patient has to endure irritation, redness and itching. Therefore there is a need for a composition that is both effective but safe, with minimal side effects.

Based on his extensive clinical experience, Dr. Goldstein has discovered that low and low-mid potency steroidal antiinflammatories can be combined with an antifungal to provide a safe and effective treatment with minimal side effects. During the interview with Examiner David Stitzel, Esq. on November 15, 2005, Dr. Goldstein presented photographs of one case study wherein the patient had presented with scaly red and inflamed, raised areas of skin infected

with inflammatory tinea. This patient had previously been treated with a variety of medications, none of which were effective. Dr. Goldstein treated the patient with a topical cream containing 0.05% desonide and 1% clotrimazole. Within a few days, the redness and swelling had disappeared, leaving the skin looking almost normal in the photographs. A copy of the photographs is enclosed with this Appeal Brief (Appendix).

The data presented at the November 15, 2005 interview demonstrated the unexpected efficacy and lack of side effects of one non-halogenated steroidal anti-inflammatory, desonide, in combination with an antifungal. Additional data showing the same unexpected efficacy and lack of side effects for other members of the claimed class of low to low-mid potency steroidal antiinflammatories is provided in the Declaration under 37 C.F.R. § 1.132 by Dr. Goldstein submitted with the Amendment and Response on March 14, 2007, a copy of which is enclosed with this Appeal Brief (Appendix).

I. Claims rejected under 35 U.S.C. § 102

Legal Standard

For a rejection of claims to be properly founded under 35 USC §102, it must be established that a prior art reference discloses each and every element of the claims. *Hybritech Inc v Monoclonal Antibodies Inc*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 US 947 (1987); *Scripps Clinic & Research Found v Genentech Inc*, 18 USPQ2d 1001 (Fed. Cir. 1991). The Federal Circuit held in *Scripps*, 18 USPQ2d at 1010:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. . . *There must be no difference* between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. (Emphasis added)

A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation. As the Federal Circuit held in *Scripps, Id.*:

> [A] finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill in the gaps in the reference.

In the present case, the examiner has adopted the position that, having the answer in hand, that of selecting a narrow class of low to low-medium potency steroidal anti-inflammatory compounds, and combining this with an antifungal, the prior art discloses the claimed subject matter through its disclosure of ***all*** of the steroidal anti-inflammatory compounds in combination with an antifungal. The courts have held, however, that the disclosure of a broad genus does not disclose a narrow selection, where that narrow selection has properties that could not be predicted from the properties as a whole.

In *Air Products* , the district court stated that "a prior art reference which contains a broad general disclosure requiring guessing, testing, speculation or 'picking and choosing' from an encyclopedic disclosure will not anticipate." 219 U.S.P.Q. at 231 (citing *In re Arkley*, 59 C.C.P.A. 804, 455 F.2d 586 (C.C.P.A. 1972)) (in order to anticipate, a piece of prior art "must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference"); *In re Samour*, 571 F.2d 559, 562 (C.C.P.A. 1972); and *General Battery Corp. v. Gould, Inc.*, 545 F. Supp. 731, 740 (D. Del. 1982)). In *In re Arkley* , 59 C.C.P.A. 804, 455 F.2d 586 (Cust. Pat. App.1972), the Court of Customs and Patent Appeals held that the disclosures of the cited prior art must be sufficiently clear that a person of ordinary skill in the art would understand their full implication without resorting to speculation or guesswork. 455 F.2d at 587.

In *General Battery*, the court noted that a prior art reference "must contain within its four corners, adequate directions for the practice of the patent claim sought to be invalidated." 545 F. Supp. at 744 (internal quotation marks and citation omitted). "Unless all of the same elements are found in exactly the same situation and united in the same way to perform the identical function in a single prior art reference, there is no anticipation." *Id.* (internal quotation marks and citation omitted). In analyzing the prior art reference cited by the defendant, the court found that the references which in combination allegedly anticipate the [patent-in-suit] are scattered throughout the work. One would have to pick and choose among various pages in Vinal to piece together a

battery such as that claimed in the patents in suit. This process of selection would require some inventive skills to determine by simply reading Vinal's book that adding sodium sulfate in a conditioning amount to a moist battery would enhance the shelf life of that battery. The elements of the invention are not in the same location nor are adequate directions provided to manufacture the invention.

The prior art, as discussed in more detail below, does not disclose selecting the claimed class of steroidal anti-inflammatory in combination with an antifungal as required by the claims.

(1) Claims 1 and 8-13

Quigley describes topical compositions useful in treating fungal diseases that comprise an antifungal agent and an anti-inflammatory steroid. See, e.g., column 2, line 66-column 3, line 27. The compositions are stated to possess a so-called synergistic effect when the anti-inflammatory steroid is ester bearing. Id. The anti-inflammatory steroids useful in the composition of Quigley are exemplified in a list of steroids classified by potency. Id., column 4, line 52-column 62.

Quigley describes prophetic formulations according to that invention. See Tables A-H and their accompanying text. Quigley also provides working Examples 1-11 that are stated to describe various formulations that were prepared. All of the prophetic formulations and those described in the working examples either prophetically prefer or are stated to contain betamethasone dipropionate as the anti-inflammatory steroid. Neither the prophetic formulations nor the exemplified compositions constitute an anticipation of claim 1.

Turning to the prophetic formulations first, it is seen that the steroid may be contained in these formulations in an amount of 0.01-2.5 wt%, preferably 0.01-0.1wt%. Formulations containing betamethasone dipropionate in these amounts are stated by Quigley to range in potency from Class 1 (highest potency) to Class 5 (low-medium potency). Thus, in order to arrive at formulations within the scope of claim 1 from the myriad of the formulations described in the prophetic examples of Quigley would require significant picking and choosing. As set forth in *In re Arkley* (59 C.C.P.A. 804, 455 F.2d 586 (C.C.P.A. 1972)), a prior art reference which contains a broad general disclosure requiring guessing, testing, speculation or 'picking and choosing' from an encyclopedic disclosure will not anticipate.

Now turning to the examples of Quigley, it is seen that that the formulations of Examples 1-12 contain 0.064 wt% of betamethasone dipropionate. Example 13 only states that a "test formulation" was used. Based upon the amount of the betamethasone dipropionate, these formulations appear to be in Class 1, 2 and 3 of Quigley and thus are more potent than the compositions of claim 1. Even the lotion of Example 10 of Quigley contains 0.064 wt% betamethasone dipropionate. This is equivalent to the amount of betamethasone dipropionate in Lotrisone™ cream that is stated to be very potent at pages 1-2 of the specification. In this regard, note that the betamethasone dipropionate lotion stated by Quigley to be of low-medium potency at column 5, line 30, contained only 0.02% of the steroid. Thus, the examples of Quigley are directed to formulations that are more potent than those of claim 1.

There is no recognition that the potency of the steroidal anti-inflammatory is the cause of the side effects and can be eliminated not by changing the carrier as suggested by Quigley but by selecting a narrow class of steroidal anti-inflammatories. Accordingly, claim 1 is novel over Quigley. Claims 8-13, which depend from claim 1, are novel over Quigley for at least the reasons discussed above.

(2) Claims 1-3, 8-13, and 17

Burnett describes anhydrous compositions for topical delivery of a medicament containing (a) a penetration enhancer/solvent selected from the group consisting of alcohol, propylene glycol, or a combination thereof; (b) a humectant/solvent selected from the group consisting of polyethylene glycol, glycerin, sorbitol, xylitol, or combinations thereof; an anhydrous vehicle; and (d) one or more medicaments (abstract). With respect to Example 1, Burnett alleges that the compositions delivered greater amounts of ketoconazole and desonide to the epidermis and dermis, but less to the receptor versus commercially known formulations such as NIZORAL® and DesOwen® (page 8, paragraph 0036). Burnett alleges that this may clinically translate to lower systemic absorption of the active agents, thereby lowering systemic active agent toxicity (page 8, paragraph 0036).

Burnett requires the use of a penetration enhancer. See abstract and col. 2, lines 9-11. There is a description of a formulation that contains, in addition to a carrier and penetration enhancer, 0-2% ketoconazole and 0-0.05% desonide (see tables 1-4, 7-10).

As discussed at pages 14-16 of the Amendment and Response file on December 18, 2008 and incorporated herein by reference, the carrier can alter the potency of the applied steroidal anti-inflammatory and antifungal. Not only is this an issue when one includes a penetration enhancer, but the use of a penetration enhancer causes the steroidal anti-inflammatory to penetrate into the dermis, leading to higher potency of the anti-inflammatory and risking the side effects Appellants avoid. Further, the use of a penetration enhancer also causes the anti-fungal portion of the composition to be less efficacious at the epidermis, which is the site of the fungal infection.

Referring to Appellants' specification, paragraph 3 of the application teaches away from a formulation where the anti-inflammatory penetrates into the dermis: "Steroids can penetrate the skin and cause undesirable side effects, including skin atrophy, hypopigmentation, suppression of the hypothalamic-pituitary-adrenal axis, Cushing's syndrome, and appearance of telangectasias." Paragraph 8 states "The composition can be formulated in any dosage form suitable for topical administration." The result is that one would select a carrier that is topical (i.e., applied to the epidermis) and which does not cause the steroids to penetrate the skin and cause undesirable side effects. This limitation is explicit in the claims.

Therefore, Burnett does not disclose or suggest compositions containing a therapeutically effective amount of a low to low-medium potency steroidal anti-inflammatory causing minimal skin atrophy, striae and hypopigmentation, in a concentration between 0.01 wt% and 5.0 wt%, and having a higher potency than 1 wt% hydrocortisone, and wherein the composition does not

cause the steroids to penetrate the skin and cause undesirable local side effects as required by claim 1. Accordingly, claim 1 is novel over Burnett. Claims 2, 3, 8-13, and 17, which depend from claim 1, are novel over Burnett for at least the reasons discussed above.

II. Claims rejected under 35 U.S.C. § 103

Legal Standard

The starting point for an obviousness determination must be the Supreme Court's decision in *KSR v. Teleflex,* 550 U.S. 398 (2007), which refocuses the determination of whether a claimed invention is obvious back to the process the Court had defined in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966). There, the Court had held that the obviousness determination should address four factors, all of which must be considered, though not in any prescribed order: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any secondary considerations suggesting nonobviousness, such as commercial success, failure of others, and long felt but unmet need. *Id.* The Court cautioned that the fact finder should be careful about reading the teachings of the invention at issue into the prior art, to avoid applying inappropriate hindsight, *ex post* reasoning. *Id. at 36.*

In *KSR*, the Court reversed a decision of the Federal Circuit that it characterized as having applied too mechanistically the role of "teaching, suggestion, motivation" ("TSM") in the prior art to combine references, to the exclusion of any consideration of other factors, such as the general knowledge and creativity of a person of ordinary skill in the art, or the competitive

pressures to solve the problem addressed by the invention, that may provide the motivation to combine elements. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 407 (U.S. 2007). Thus, while TSM should not be abandoned, it must not become a mantra that precludes consideration of other evidence relevant to whether it would have been obvious to combine prior art to achieve the result claimed by the inventors. The Supreme Court held that where a skilled artisan merely pursues "known options" from a "finite number of identified, predictable solutions," obviousness under § 103 arises. 550 U.S. at 421. Section 103 bars patentability unless "the improvement is more than the predictable use of prior art elements according to their established functions." 550 U.S. at 417. However, "where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness." *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009).

Even where the prior art suggests or motivates an inventor to develop the composition or process at issue, the Federal Circuit continues to recognize that there is a critical question under 35 U.S.C. § 103 as to whether the combined teachings of the prior art "would have given rise to a reasonable expectation of success" in achieving what is claimed. *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007), *petition for cert. denied*, 7128 S. Ct. 1655, 170 L. Ed. 2d 355, 2008. There, the inventors merely used routine research methods to prove what was already believed to be the case and had not made a patentable invention. *Id.* at 1363-64. However, the court noted that a different case is presented if all the prior art suggested was to explore a general approach and gave only general guidance as to the particular form of the

claimed invention or how to achieve it. *Id.* at 1364-65 (citing *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988), and *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1166-67 (Fed. Cir. 2006), as continuing to provide useful guidance in determining whether the expectation of success from a line of inquiry found in prior art is so great as to make a resulting invention obvious).

Where the art is unpredictable, the element of "identified, predictable solutions" "may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." *Eisai, supra,* Slip Op. at 8. Considering all of these factors, the Federal Circuit in *Eisai* affirmed summary judgment that the patent claiming rabeprazole was not an obvious modification of a prior art compound.

(3) Claims 1-3 and 7-17

In order to establish a *prima facie* case of obviousness, the references, alone or in combination, must disclose each and every element of the claims. As discussed above, Quigley does not disclose or suggest compositions containing a therapeutically effective amount of an antifungal compound for treating a fungal disease or a pharmaceutically acceptable salt thereof; and a therapeutically effective amount of a low to low-medium potency steroidal anti-inflammatory causing minimal skin atrophy, striae and hypopigmentation as required by the claims. The Examiner has failed to establish a *prima facie* case of obviousness for at least the reasons discussed above.

Further, Appellants have presented data which clearly shows the criticality of the small set of steroidal anti-inflammatories specified in the claims and shows unexpected results across

this small set (*see* the declaration of Dr. Jay Goldstein submitted with the Amendment and Response filed on June 1, 2006, a copy of which is enclosed). Dr, Goldstein's declaration is discussed in detail at pages 14-16 in the Amendment and Response filed on December 18, 2009. That discussion is incorporated herein by reference.

As Dr. Goldstein's declaration establishes, many of the patients had previously been treated with strong anti-inflammatory steroids. Counter-intuitively, the stronger anti-inflammatory creates more inflammation, not less, and thinning of the skin. This demonstrates a long standing but unmet need for effective and safe formulations that minimize side effects. The data in Dr. Goldstein's declaration not only demonstrates the unexpected efficacy and lack of side effects of one non-halogenated steroidal anti-inflammatory, desonide, in combination with an antifungal but additional data is presented showing the same unexpected efficacy and lack of side effects for other members of the claimed class of low to low-mid potency steroidal anti-inflammatories. Members of the claimed class that have been shown to produce results comparable to a topical cream containing 0.05% desonide and 1% clotrimazole are:

Clotrimazole 1% cream with alclometasone dipropionate 0.05% cream applied twice daily;

Oxicanozole cream 1% with Hydrocortisone cream 2½% applied twice daily;

Econazole cream 1% with fluocinalone acetonide cream 0.01% applied twice daily; and

Econazole cream 1% with alclometasone dipropionate 0.05% applied twice daily.

This data is comparative data, since the patients were initially treated with high potency steroidal anti-inflammatories in combination with antifungal agents. The unexpected efficacy of the small class of claimed low to low-medium potency steroidal anti-inflammatories in combination with an antifungal could not have been predicted in view of the prior art, which, to the extent it provides any teaching other than a "grocery list of compounds", teaches away from using weaker anti-inflammatories.

A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicants. The degree of teaching away will of course depend on the particular facts; in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant. *In re Caldwell*, 50 C.C.P.A. 1464, 319 F.2d 254, 256, 138 U.S.P.Q. (BNA) 243, 245 (CCPA 1963) (reference teaches away if it leaves the impression that the product would not have the property sought by the applicant).

As discussed above, Quigley describes, in the working examples, creams, ointments, and gels containing betamethasone dipropionate. As shown in the table at columns 4 and 5, the formulations described in the examples are classified as high potency or medium-high potency formulations. Example 12 describes the evaluation of betamethasone containing cream, which again is a high potency formulation. One of ordinary skill in the art reading Quigley would be motivated to prepare high or medium-high potency formulations, not the low or low-medium

potency formulations required by the claims, and thus would be lead in a direction divergent from the path Appellants have taken.

Accordingly, claim 1 is not obvious over Quigley. Claims 2, 3, and 7-13 and 17, which depend from claim 1, are not obvious over Quigley for at least the reasons discussed above.

Claims 14-16 are drawn to a method of treating a fungal disease comprising administering to a subject in need thereof the composition of any of claims 1-13 or 17, with a thin application of the composition two times per day to the affected areas. For the reasons discussed above with respect to claims 1-3, 7-13, and 17, claims 14-16 are not obvious over Quigley.

(4) Claims 1-13 and 17

Burnett is discussed above. Burnett does not disclose or suggest compositions containing a therapeutically effective amount of a low to low-medium potency steroidal anti-inflammatory causing minimal skin atrophy, striae and hypopigmentation, in a concentration between 0.01 wt% and 5.0 wt%, and having a higher potency than 1 wt% hydrocortisone, and wherein the composition does not cause the steroids to penetrate the skin and cause undesirable local side effects as required by claim 1 and the claims dependent thereon

Shah describes a gel formulation comprising an imidazole antifungal agent, either by itself or in combination with a steroid anti-inflammatory agent. Id., column 3, lines 10-16. A litany of anti-inflammatory steroids is listed at column 3, line 54-column 4, line 2. A preference for mid-potency steroids is expressed at column 4, lines 3-16 of Shah. In fact, Shah discloses

that mid-potency steroids are preferred in view of certain disadvantages of strong and low-potency steroids including undesirable side effects such as skin atrophy, rebound phenomenon, and telangiectasia and the fact that low potency steroids may fail to provide fast relief from inflammatory symptoms (col. 4, lines 3-11). Shah does not cure the deficiencies of Burnett. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness.

Further, Appellants have presented data which clearly shows the criticality of the small set of steroidal anti-inflammatories specified in the claims and shows unexpected results across this small set (*see* the declaration of Dr. Jay Goldstein submitted with the Amendment and Response filed on June 1, 2006) a copy of which is enclosed and is discussed in detail above.

Accordingly, claim 1 is not obvious over Burnett in view of Shah. Claims 2-13 and 17, which depend from claim 1, are not obvious over Burnett in view of Shah for at least the reasons discussed above.

SUMMARY AND CONCLUSION

In summary, Appellant has demonstrated that the claimed combination unexpectedly provides efficacy and safety, which is neither disclosed by, nor recognized or suggested in the prior art. Allowance of all claims 1-17 is earnestly solicited.

Respectfully submitted,

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Date: November 13, 2009

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APPENDIX: CLAIMS

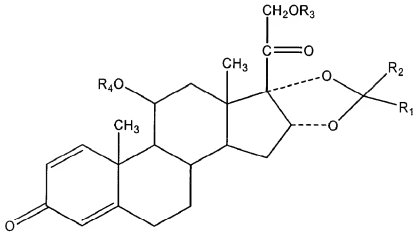
1. (previously presented) A topical antifungal composition comprising:

a) a therapeutically effective amount of an antifungal compound for treating a fungal disease or a pharmaceutically acceptable salt thereof; and

b) a therapeutically effective amount of a low to low-medium potency steroidal anti-inflammatory causing minimal skin atrophy, striae and hypopigmentation, in a concentration between 0.01 wt% and 5.0 wt%, and having a higher potency than 1 wt% hydrocortisone, and

c) a carrier suitable for administration of the antifungal compound and the steroidal anti-inflammatory to the skin, wherein the composition does not cause the steroids to penetrate the skin and cause undesirable local side effects.

2. (previously presented) The antifungal composition of claim 1 wherein the steroidal anti-inflammatory has the following structure:



wherein R_1, R_2, R_3, and R_4 taken independently can be H, C1-C10 alkyl, C1-C10 alkenyl, C3-C10 cycloalkyl, and phenyl groups; R_1 and R_2 taken together can be C3-C10 cycloalkyl; and R_3 and R_4 taken independently can be H, C1-C10 alkyl, C1-C10 alkenyl, C3-C10 cycloalkyl, phenyl, C7-C10 phenylalkyl, carboxylate, sulfonyl, phosphoryl, and phosphonyl groups.

3. (previously presented) The composition of claim 2 wherein R_1, R_2, R_3, and R_4 groups are independently H, CH_3 , ethyl, propyl, phenyl, and phenylmethyl groups.

4. (previously presented) The composition of claim 1 wherein the steroidal anti-inflammatory is desonide and the antifungal compound is clotrimazole.

5. (previously presented) The composition of claim 4 containing 0.01 wt % to 5.0 wt % desonide.

6. (original) The composition of claim 5 containing 0.1 wt % to 5 wt % clotrimazole.

7. (previously presented) The composition of claim 1 wherein the steroidal anti-inflammatory is selected from the group consisting of Fluocinolone acetonide, Hydrocortisone valerate, Hydrocortisone butyrate, Alclometasone dipropionate, Desonide, and hydrocortisone probutate.

8. (original) The composition of claim 1 wherein the antifungal is selected from the group consisting of polyene type antifungal agents and azole type antifungal agents.

9. (original) The composition of claim 8 wherein the antifungal is selected from the group consisting of Amphotericin B, Nystatin, Flucytosin, Natamycin, Ketoconazole,

Econoazole, Miconazole, Itraconazole, Fluconazole, Econazole, Clotrimazole, Griseofulvin, Oxiconazole, Terconazole, Tioconazole, Clotrimazole, Silver Sulfadiazine, Ciclopirox olamine, and Terbinafine.

10. (original) The composition of claim 1, wherein the composition is formulated as a cream, ointment, gel, lotion, foam, powder, aerosol, spray, shampoo, or liquid solution.

11. (original) The composition of claim 10 having a pH of about 3.5 to about 7.0 further comprising: at least one solvent, at least one emollient, at least one humectant, at least one preservative, and at least one emulsifier; and optionally including an acid, base, or buffering agent to adjust the pH.

12. (original) The composition of claim 11, wherein the solvent is selected from the group consisting of propylene glycol, butylene glycol, hexylene glycol, polyethylene glycols, polypropylene glycols, and polyurethane compounds; the emollient is selected from the group consisting of white petrolatum, mineral oil, propylene glycol dicaprylate, lower fatty acid esters and lower alkyl ethers of propylene glycol, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, stearic acid, cetyl esters wax, spermaceti wax, and white wax; the humectant is selected from the group consisting of glycerin and sorbitol; and the emulsifier is selected from the group consisting of glyceryl monostearate, glyceryl monoleate, stearic acid, polyoxyethylene cetyl ether, polyoxyethylene cetostearyl ether, polyoxyethylene stearyl ether, and polyethylene glycol stearate; wherein the optional acid is selected from the group consisting of hydrochloric acid and phosphoric acid, the optional base is chosen from diethanolamine, triethanolamine, and sodium

hydroxide, the optional buffering agent is chosen from monobasic sodium phosphate and dibasic sodium phosphate, and the preservative is chosen from benzyl alcohol, sodium benzoate and parabens.

13. (original) The composition of claim 1 wherein the antifungal is in an amount effective to treat fungal disease selected from the group consisting of tinea pedis, tinea capitis, tinea corporis, tinea versicolor, scalp disorders, tinea cruris, and candidiasis.

14. (previously presented) A method of treating a fungal disease comprising administering to a subject in need of treatment the composition of any of claim 1-13 or 17, with a thin application of the composition two times per day to the affected areas.

15. (original) The method of claim 14 wherein the subject is a child of under 10 years old.

16. (original) The method of claim 14 wherein the fungal disease is selected from the group consisting of tinea pedis, tinea capitis, tinea corporis, tinea versicolor, scalp disorders, tinea cruris, and candidiasis.

17. (previously presented) The composition of claim 1 wherein the steroidal anti-inflammatory is not halogenated.

APPENDIX: EVIDENCE

Declaration under 37 C.F.R. § 1.132 by Dr. Goldstein

Copy of photographs submitted with the Declaration under 37 C.F.R. § 1.132 by Dr. Goldstein

National Psoriasis – Potencies of Topical Steroids

APPENDIX: RELATED PROCEEDINGS

There are no related proceedings.